Intrathecal Gene Therapy for the Treatment of Leptomeningeal Carcinomatosis

Scientific Abstract

Meningeal carcinomatosis occurs in 5% to 20% of all cancer patients. Most adult cases are due to breast or lung carcinomas. Over recent years the incidence of meningeal carcinomatosis has been reported to increase, perhaps since cancer patients survive longer with improved systemic therapy. Patients with meningeal carcinomatosis have an exceedingly poor prognosis. When maximal therapy is tolerated (intrathecal methotrexate and whole-brain irradiation) mean survival is limited to 6-7 months and fewer than 15% of the patients are alive at one year. In an attempt to improve this grim prognosis of patients with leptomeningeal carcinomatosis, we have developed a novel approach for the treatment of this disease. This approach makes use of recombinant DNA technology to transfer a sensitivity gene into the malignant cells seeding the leptomeninges. This is achieved by direct intrathecal injection of cells that actively produce a retroviral vector carrying the herpes simplex thymidine kinase gene (HStk), which sensitizes the cells to the antiviral drug Ganciclovir (GCV). The intrathecally injected producer cells and vector particles can circulate in the CSF and infect cells that are actively synthesizing DNA. In the subarachnoid space, such cells are predominantly tumor cells. The HS-tk gene is incorporated into the genome of tumor cells and results in expression of the protein encoded by the gene. The enzymatic interaction between HS-tk and GCV leads to the production of toxic triphospates of GCV that interfere with DNA synthesis and result in the death of the tumor cells. Since the thymidine kinase enzyme which is normally present in mammalian cells has very low affinity for GCV, systemic toxicity related to this mechanism is not expected.

The proposed clinical trial will evaluate the dynamics of retroviral vectors in the subarachnoid space, assess the safety of this approach and evaluate its potential antitumor efficacy. This is a dose-escalating study where increasing numbers of producer cells will be injected into the ventricular system and the spinal subarachnoid space. Indications of antitumor efficacy will include monitoring of clinical symptoms, craniospinal MRI evaluation, and CSF analysis for cytology and tumor markers. A total of 20 patients will be enrolled in the various phases of the study.

This is the first clinical attempt to treat meningeal carcinomatosis by *in vivo* , intrathecal, genetic manipulation of the tumor's genome.